EDITORIAL

Does testosterone therapy raise the risk of VTE?

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TESTOSTERONE REPLACEMENT THERAPY IS INCREASINGLY PRESCRIBED IN BOTH PRIMARY AND secondary care. The only unequivocal indication for testosterone treatment is pathological hypogonadism. The majority of men diagnosed with hypogonadism are identified during investigations for sexual dysfunction, most notably erectile dysfunction. Concern has been raised, however, about the cardiovascular risks of testosterone treatment, particularly in those men without pathological hypogonadism.

In the United States, the FDA has placed a warning on all testosterone products regarding increased risk of venous thromboembolism (VTE) after testosterone treatment. However, studies have reported contradictory results on the association between testosterone treatment and VTE.

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This large observational study used data from 370 UK general practices participating in the Clinical Practice Research Datalink (CPRD).[1] Data on all men aged 20-89 years were analysed, between January 2001 and May 2013.

All cases of VTE (both deep vein thrombosis and pulmonary embolism) were identified in the study population, and classified according to the presence of additional risk factors: cancer, surgery, trauma, acute medical conditions in the 90 days preceding the VTE and a history of cancer more than 90 days before the index day. Up to 50 controls, matched by age and risk factors, were selected for each case.

Three testosterone treatment groups were analysed: current treatment, recent but not current treatment, and no treatment in the previous two years.

The source population was 2.92 million men, and from this, with 12.1 million person-years of follow-up, 19,246 men had a confirmed VTE, an incidence rate for VTE of 15.8 per 10,000 person-years.

Overall, 69 VTEs (0.36%; 28 deep vein thromboses and 41 pulmonary embolisms) occurred during current testosterone treatment and 22 (0.11%; 7 deep vein thromboses and 15 pulmonary embolisms) after recent treatment.

The cases and controls were identical in age and the predefined matching, but interestingly the cases were more often obese and had more comorbidities such as polycythaemia, chronic pulmonary disease, heart failure, MI and peripheral vascular disease.

The adjusted rate ratio (RR) of VTE was 1.25 (95% CI: 0.94-1.66) for current versus no testosterone treatment. In the first six months of testosterone treatment, the RR of VTE was 1.63, corresponding to 10 additional VTEs above the base rate of 15.8 per 10,000 person-years. This increase disappeared after more than six months' treatment with testosterone and after treatment cessation. The rate of VTE was also seen to be higher in those on testosterone without a formal diagnosis of pathological hypogonadism (RR 1.88 vs 1.52).

The study results suggest a transient increase in the risk of VTE, peaking during the first three to six months after initiation of testosterone treatment. This risk was seen to be stronger in those without known risk factors for VTE (RR 1.91 vs 1.41). However, the results from this study must be interpreted with caution. Despite the huge source population, VTE is a relatively uncommon event, and VTE in men taking testosterone a rare event – thus, despite analysing more than 19,000 men with VTE, only 69 cases (0.36%) were in men currently being treated with testosterone – this significantly weakens the overall analysis, and the subgroup analysis still further.

So what are the lessons for primary care? The evidence remains inconclusive as to whether testosterone increases the risk of VTE significantly. However, it would appear sensible, if initiating testosterone replacement, particularly in those with a past history of VTE or other significant risk factors, to mention the concern over this, and advise early reporting of any potential symptoms of VTE.

Furthermore, it emphasises the need to initiate testosterone therapy only for those with confirmed pathological hypogonadism, and to remind patients that use of testosterone replacement by those with normal testosterone levels (e.g. to improve sexual function or vitality/energy) is not only without evidence of benefit but also with some significant potential risks to health.

REFERENCE
1 Martinez C, Suissa S, Rietbrock S et al. Testosterone treatment and risk of venous thromboembolism: population based case-control study. *BMJ* 2016;355:i5968

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